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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,476	01/18/2001	Irina A. Buhimschi	BUH385-00/01003A	9887

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DANIEL S. HODGINS
JACKSON WALKER, LLP
112 E. PECAN ST.; 2100
SAN ANTONIO, TX 78205

EXAMINER	
SNEDDEN, SHERIDAN	

ART UNIT	PAPER NUMBER
1653	11

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,476	BUHIMSCHI ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *6,10,11 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9 and 12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of invention I, claims 1-21 is acknowledged. Applicant further elects N-acetylcysteine to be examined within the scope of invention I. Thus, claims 6, 10, 11 and 20-21 directed to non-elected invention (e.g., spin trapping compounds) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. No generic or linking claim is currently allowable. Election was made **without** traverse in Paper No. 10. Applicant's cancellation of claim 22 is acknowledged. Claims 1-5, 7-9, 12-19, as they relate to election of N-acetylcysteine, are under examination.

Drawings

2. The Draftsman has approved drawing sheets 1-9 submitted on 1/18/2001.

Information Disclosure Statement

Applicant is advised that additional sheets of the PTO-1449 of Paper No: 7, filed 7/2/02 appear to be missing from the application. Additional sheets of PTO-1449 would be considered upon resubmission and required for consideration of all submitted references.

Claim Rejections - 35 USC § 112

3. Claims 1 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent for reducing the occurrence of premature labor, does not reasonably provide enablement for an agent which prevents premature labor. In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure

meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, applicants are claiming a method for "preventing" premature labor in an animal. (Factors 1, 6) The nature of the invention is of a pharmaceutical for the treatment of a disease, *i.e.* premature labor. As stated, however, the claim asserts that the composition is capable of preventing premature labor, or to keep from happening. (Factor 2) The state of the art does not teach the absolute prevention of premature labor, but that most therapies are ineffective for the prevention of premature labor (see Goldenberg; Obstet Gynecol 2002 Nov;100(5 Pt 1):1020-37). (Factor 3) Goldenberg teaches that the etiology of preterm labor is not clear and therapies ineffective, thus any claim to the prevention of premature labor is highly unpredictable given the current state of the art. (Factors 4, 5) Furthermore, applicant states that the invention may be used in the prevention of premature labor and provides a scientific explanation the biological mechanisms involved. Whereas examples are given for the reduction of the occurrence of premature labor, prevention is not taught. On page 32 of the specification, the Applicant demonstrates that the effect of treatment was the increased survival rate, not absolute prevention. (Factors 6,7) The courts have interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of

sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Based on the state of the prior art and the level of guidance in the specification, a person of ordinary skill in the art would still be required to conduct undue experimentation to practice the full breadth of the claims, which is a method for the absolute prevention of premature labor. (Factor 8) The level of skill in the art required is considered to be a PhD professional with several years experience.

Because neither the prior art nor the current application provides sufficient guidance to one of even ordinary skill in the art as to the entire breadth of the claims which is the prevention of premature labor, the quantity of experimentation for such a claim is considered to be undue and thus, not enabled. This rejection also applies to claim 7 directed toward the preventing premature rupture of membranes.

4. Claims 1 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using a free radical scavenger, *e.g.* NAC, for reducing the occurrence of premature labor, does not reasonably provide enablement for any agent which induces the production of endogenous free radical scavenger. In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention:

The nature of the invention is a method of therapy for premature labor by the administration of a free radical scavenger, e.g. NAC, or other agents that would reduce oxidant stress and improve the outcome of premature labor.

The breadth of the claims:

The claims are directed toward the administration of a free radical scavenger, a precursor thereto, or any agent which induces the endogenous production of a free radical scavenger.

The amount of direction or guidance present and the presence or absence of working examples:

Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). In the instant case, the specification does not teach or provide examples of all agents that would induce endogenous production of free radical scavenger in the method of treating premature labor.

The state of the prior art and the predictability or lack thereof in the art:

The prior art teaches many agents which would have the result of inducing the endogenous production of a free radical scavenger. For example, Sander *et al.* teach that Candid albicans, an opportunistic fungal pathogen, is able to produce large amounts of reactive oxygen species. Therefore, Candid albicans would qualify as an agent inducing production of endogenous free radical scavenger.

It is unlikely that the administration of Candid albicans would result in the successful treatment of preterm labor. Therefore, the use successful treatment of preterm labor with any agent that induces endogenous production of a free radical scavenger is unpredictable.

The quantity of experimentation needed:

The courts have interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). As such, the quality of experimentation necessary to establish a method of treating preterm labor with all agents that induce the endogenous production of a free radical scavenger is undue.

Because neither the prior art nor the current application provides sufficient guidance to one of even ordinary skill in the art as to the entire breadth of the claims which is the prevention of premature labor, the quantity of experimentation for such a claim is considered to be undue and thus, not enabled

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-9, 12-19 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependent claims thereto are indefinite as the claims refer to an effective amount but do not indicate what is the effective amount. Note that simply administering, as is claimed, does not per se nor necessarily result in treatment of preterm labor, thus the claim would appear to be incomplete.

Claims 8 and 19 are indefinite for the recitation of non-elected subject matter.

Claim 12 is indefinite for use of the abbreviation 'ROS.' See also PPROM is claim 18.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 7, 9, 12-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Stamler *et al.* (US Patent 5,648, 393). Stamler *et al.* teach the use of low molecular weight S-nitrosothiols, such as S-nitroso-N-acetylcysteine (a modified N-aceytlcysteine) and S-nitroso-glutathione, to relax non-vascular smooth muscle (column 1, lines 22-32). With regards to the method of therapy for perterm labor, Stamler *et al.* teach the administration of a therapeutically effective amount to an animal (regarding claims 13-17) of an S-nitrosothiol compound as

mentioned above to relax uterine smooth muscle and that increased contractility of uterine smooth muscle precipitates premature labor (see column 4, line 34-37, column 11, lines 58-65). As S-nitroso-N-acetylcysteine would qualify as a free radical scavenger or antioxidant as it is reactive with oxygen, the teaching above anticipates claims 1, 4, 5, 7, 9, 12-19.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-5, 7-9 and 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler *et al.* (US Patent 5,648,393) in view of Lamont (Eur J Pediatr. 1999) and Katz *et al.* (Clin Obstet Gynecol. 1999). Stamler *et al.* teach the therapy for premature labor by the administration of a free radical scavenger as discussed above.Stamler *et al.* teach the use of low molecular weight S-nitrosothiols, such as S-nitroso-N-acetylcysteine and S-nitroso-glutathione, to relax non-vascular smooth muscle (column 1, lines 22-32). With regards to the method of therapy for perterm labor, Stamler *et al.* teach the administration of a therapeutically effective amount to an animal (regarding claims 13-17) of a S-nitrosothiol compound as mentioned above to relax uterine smooth muscle and that increased contractility of uterine smooth muscle precipitates premature labor (see column 4, line 34-37, column 11, lines 58-65). As S-nitroso-N-acetylcysteine would qualify as a free radical scavenger or antioxidant as it is reactive with oxygen, the teaching above anticipates claims 1, 5, 7, 9, 12-19.

Stamler *et al.* does not expressly teach the use of N-acetylcysteine in a method for therapy of preterm labor (regarding claims 4 and 8). However, in figure 13, Stamler *et al.* demonstrates that the relaxant effect of S-nitroso-N-acetylcysteine is significantly greater than that of N-acetylcysteine. Whereas the invention of Stamler *et al.* teach the preference for S-nitroso-N-acetylcysteine, the use of N-acetylcysteine is suggested to be effective in the therapy. Therefore, the invention of Stamler *et al.* encompasses the administration of N-acetylcysteine for the treatment or prevention and the person of ordinary skill in the art would have been motivated as expected success to use N-acetylcysteine in the method of therapy for preterm labor based on the teachings of Stamler *et al.*

Lamont teach that infection is a well recognized cause of spontaneous preterm labor and that antibiotics are commonly administered as a prophylactic (see Abstract; regarding claim 2).

Katz *et al.* teach the use of tocolytic agents for stopping uterine contractions and therefore delay delivery or premature labor (see Abstract; regarding claim 3).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to add an antibiotic or a tocolytic agent to the method of therapy for premature labor by the administration of a free radical scavenger taught by Stamler *et al.*. The person of ordinary skill in the art would have been motivated and expected success for adding either antibiotics or a tocolytic agents to the method of therapy for premature labor as these are agents routinely used in modern therapeutic methods for preterm labor. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for regular communications to the organization where this application or proceeding is assigned is (703) 746-3975.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
December 16, 2002

SKS

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600